CLAIMS

What is claimed is:

1. A crystal of a protein-ligand complex comprising a protein-ligand complex of a truncated lck and a ligand, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex to a resolution of greater than 5.0 Angstroms; and wherein the truncated lck: (a) comprises amino acids 225 to 508 of SEQ ID NO: 1 or an amino acid sequence that differs from amino acids 225 to 508 of SEQ ID NO: 1 by only conservative substitutions; and (b) retains the globular core of the corresponding full-length lck.

2. The crystal of claim 1, wherein the truncated lck comprises an amino acid sequence of amino acids 251 to 371 of SEQ ID NO: 1, or an amino acid sequence that differs from amino acids 251 to 371 of SEQ ID NO: 1 by only conservative substitutions.

3. The crystal of claim 1 or 2, wherein the ligand is staurosporine.

4. The crystal of claim 3 having space group of $P2_12_12_1$ and a unit cell of dimensions of a = 42.2 Å, b = 73.8 Å, and c = 91.4 Å.

5. The crystal of claim 3 having space group of $P2_12_12_1$ and a unit cell of dimensions of a = 61.5 Å, b = 69.0 Å, and c = 73.7 Å.

6. The crystal of claim 1 wherein the kinase has secondary structural elements that include five beta strands and one helix in the N-terminal lobe (strands 1, 2, 3, 4 and 5 and alpha helix C), and two beta strands and seven alpha helices in the C-terminal domain (strands 6 & 8, and alpha helices D, E, EF, F, G, H and I).

7. A method of using the crystal of claim 1 in a inhibitor screening assay comprising:

(a) selecting a potential inhibitor by performing rational drug design with the three-dimensional structure determined for the crystal, wherein said selecting is performed in conjunction with computer modeling;

(b) contacting the potential inhibitor with a kinase; and

(c) detecting the ability of the potential inhibitor for inhibiting the kinase.

8. The method of claim 11, wherein detecting the ability of the potential inhibitor for inhibiting the kinase in step (c) is performed using an enzyme inhibition assay.

9. The method of claim 11, wherein detecting the ability of the potential inhibitor for inhibiting the kinase in step (c) is performed using a cellular- based assay.

10. The method of claim 11 further comprising:

(d) growing a supplemental crystal comprising a protein-ligand complex formed between the kinase and a first potential inhibitor from step (a), wherein the supplemental crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex to a resolution of greater than 5.0 Angstroms;

(e) determining the three-dimensional structure of the supplemental crystal;

(f) selecting a second potential inhibitor by performing rational drug design with the three-dimensional structure determined for the supplemental crystal, wherein said selecting is performed in conjunction with computer modeling;

(g) contacting the second potential inhibitor with a kinase; and

(h) detecting the ability of the second potential inhibitor for inhibiting the kinase.

11. A method for identifying a potential inhibitor of a kinase comprising:

(a) selecting or designing a potential inhibitor by performing rational drug design with the three-dimensional structure coordinates of any of Tables 1-5, wherein said selecting is performed in conjunction with computer modeling;

(b) contacting the potential inhibitor with a kinase; and

(c) detecting the ability of the potential inhibitor for inhibiting the kinase.

12. The method of claim 15, wherein detecting the ability of the potential inhibitor for inhibiting the kinase in step (c) is performed using an enzyme inhibition assay.

13. The method of claim 15, wherein detecting the ability of the potential inhibitor for inhibiting the kinase in step (c) is performed using a cellular- based assay.

14. The method of claim 15, wherein the potential inhibitor is designed *de novo*.

15. The method of claim 15, wherein the potential inhibitor is designed from a known inhibitor.

16. The method of claim 15 further comprising:

(d) selecting an second potential inhibitor by performing rational drug design with the three-dimensional structure coordinates of any of Tables 1-5 and the potential inhibitor of step (a), wherein said selecting is performed in conjunction with computer modeling;

(e) contacting the potential inhibitor with a kinase; and

(f) detecting the ability of the potential inhibitor for inhibiting the kinase.

17. A method of using truncated lck to grow a crystal of a protein-ligand complex comprising:

(c) contacting truncated lck with a ligand, wherein the truncated lck forms a protein-ligand complex with the ligand; and

(d) growing the crystal of the protein-ligand complex; wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex to a resolution of greater than 5.0 Angstroms.

18. The method of claim 21, wherein said growing is performed by hanging drop vapor diffusion.

19. The method of claim 21, wherein said ligand is staurosporine.

20. A method of growing a crystal of a truncated lck-ligand complex wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex to a resolution of greater than 5.0 Angstroms, comprising:

(a) contacting a truncated lck solution with a ligand, wherein the truncated lck forms a protein-ligand complex with the ligand; and

(b) growing the crystal of the protein-ligand complex; wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex to a resolution of greater than 5.0 Angstroms.

21. The method of claim 25, wherein the growing is performed by hanging drop vapor diffusion.

22. The method of claim 25, wherein the ligand is staurosporine.

23. A method of producing a crystal of a truncated lck-ligand complex wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex to a resolution of greater than 5.0 Angstroms, comprising contacting a truncated lck crystal with a ligand, wherein the truncated lck forms a protein-ligand complex with the ligand within the crystal, and wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex to a resolution of greater than 5.0 Angstroms.

24. The method of claim 28, wherein the ligand is staurosporine.

25. A method of using the three-dimensional structure coordinates of any one of Tables 1-5, comprising:

(a) Determining structure factors from the coordinates; and

(b) Applying said structure factor information to a set of X-ray diffraction data obtained from a crystal of a protein homologous to SEQ ID NO: 1;

(c) Solving the three-dimensional structure of the protein homologous to SEQ ID NO: 1.

26. A computer readable data storage material encoded with computer readable data comprising structure coordinates of any one or more of Tables 1-5.

27. A computer readable data storage material encoded with computer readable data comprising structure coordinates of the active site of any one or more of Tables 1-5.

28. A method for identifying a potential inhibitor of a kinase comprising:

(a) selecting or designing a potential inhibitor by performing rational drug design with a computer readable data storage material encoded with computer readable data comprising structure coordinates of any one or more of Tables 1-5, wherein said selecting is performed in conjunction with computer modeling;

(b) contacting the potential inhibitor with a kinase; and

(c) detecting the ability of the potential inhibitor for inhibiting the kinase.

29. A polynucleotide sequence encoding the polypeptide comprising residues 235 - 501 of SEQ ID NO.: 1, and further comprising the sequence Arg-His-His-His-His-His-His attached to residue 501 and methionine attached to residue 235, or having conservative substitutions thereof.

30. An expression vector containing the polynucleotide sequence of claim 29.

31. A host cell containing the vector of claim 29.

32. An isolated polypeptide comprising residues 235 - 501 of SEQ ID NO.: 1, and further comprising the sequence Arg-His-His-His-His-His-His attached to residue 501 and methionine attached to residue 235, or having conservative substitutions thereof.

33. An isolated polypeptide made by a method comprising the steps of:

(d) Introducing a recombinant nucleic acid encoding a polypeptide comprising residues 235 - 501 of SEQ ID NO.: 1, and further comprising the sequence Arg-His-His-His-His-His-His attached to residue 501 and methionine attached to residue 235, or having conservative substitutions thereof, into a host cell or cellular extract;

(e) Incubating the host cell or cellular extract under conditions whereby the polypeptide is expressed; and

(f) Isolating the polypeptide.

34. Use of an isolated polypeptide comprising residues 235 - 501 of SEQ ID NO.: 1, and further comprising the sequence Arg-His-His-His-His-His-His attached to residue 501 and methionine attached to residue 235, or having conservative substitutions thereof, for

growing polypeptide:inhibitor complexes comprising contacting said polypeptide with a chemical compound.

35. The use of claim 34, wherein the chemical compound is a kinase inhibitor.

36. A method for obtaining activated Lck of high homogeneity suitable for crystallization studies, comprising the steps of:

(a) contacting a stabilizer with a polypeptide comprising residues 235 - 501 of SEQ ID NO.: 1, and further comprising the sequence Arg-His-His-His-His-His-His attached to residue 501 and methionine attached to residue 235, or having conservative substitutions thereof,

(b) isolating the polypeptide comprising residues 235 - 501 of SEQ ID NO.: 1, and further comprising the sequence Arg-His-His-His-His-His-His attached to residue 501 and methionine attached to residue 235, or having conservative substitutions thereof, from unphosphorylated and multi-phophorylated variants thereof.

37. The method of claim 36, wherein the stabilizer is a polyol.

38. A stabilized form of activated Lck of high homogeneity suitable for crystallization studies, comprising (a) a polypeptide comprising residues 235 - 501 of SEQ ID NO.: 1, and further comprising the sequence Arg-His-His-His-His-His-His attached to residue 501 and methionine attached to residue 235, or having conservative substitutions thereof, and (b) a kosmotropes.

39. The activated Lck of method 38, further comprising (c) an additional stabilizing agent.